

Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1775 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

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VOL. XVIII

MAY, 1949

No. 5

PHARMACOLOGIC TESTS AS AN AID IN DIAGNOSIS OF PHEOCHROMOCYTOMA

Pheochromocytoma is a tumor of the medullary portion of the adrenal gland which produces symptoms similar to those that follow the administration of epinephrine. Large amounts of epinephrine have been found in such tumors either at necropsy or after surgical removal. Hypertension, either paroxysmal or persistent, is a salient feature. In addition a disturbance of the carbohydrate metabolism or hypermetabolism may exist with the hypertension.

The typical syndrome as a result of the release of epinephrine from a medullary adrenal tumor consists of sudden rapid rise of the blood pressure, tachycardia, great anxiety, severe headache with subsequent pallor of the face particularly, numbness, tingling and coldness of the hands and feet, sometimes nausea and vomiting, pain in the epigastrium extending into the precordial region and lastly excessive sweating.

These attacks may last from a few minutes to hours. Frequently the patients complain of weakness and exhaustion following the attacks. They may occur infrequently and may be mild at first but may become more frequent and more severe as the condition is prolonged. Severe attacks may lead to death from cerebral hemorrhage, shock or pulmonary edema. The typical syndrome is rather well-defined, but in any individual case one or more of the symptoms may be lacking which would aid in the diagnosis of pheochromocytoma.

The differentiation of this syndrome from such clinical conditions as coronary occlusion, hyperthyroidism, histaminic cephalgia, migraine, menopausal states, anxiety states, and persistent hypertension may be difficult. The most confusing patients are the hyperreactors and those who have essential hypertension and whose blood pressure is extremely labile. Patients who have anxiety states also cause difficulty because of their frequent description of attacks or spells of various kinds.

In the past the diagnosis of suspected pheochromocytoma has been based on (1) demonstration of a tumor by palpation or roentgenologic examination, (2) the localization of such a tumor by perirenal insufflation of air as introduced by Cahill and later used by others, (3) the presence of a pressor substance in the blood which was first demonstrated by Beer, King and Printzmetal and (4) observation of the attacks which characterize this clinical entity.

Previously, in order to make the diagnosis, these attacks were precipitated by various means, including physical exertion, change in position, such as

rising from the recumbent to the upright position, turning on the side of the tumor, massage of the abdomen on the side of the tumor and administration of insulin or epinephrine. Hyman and Mencher also produced attacks of paroxysmal hypertension by the cold pressor test and by injection of histamine. However, they failed to mention whether they considered the latter a suitable means for voluntary production of an attack. Because no tumor may be demonstrated and a reliable method for demonstrating epinephrine in the blood is still not available, the observation of patients in attacks is of primary importance. Since none of the methods of inducing attacks was dependable and since the opportunity to observe the patient in a spontaneous attack might not present itself, it was apparent that a simple pharmacologic procedure that would induce attacks at will would be of great help in diagnosis.

Histamine Test

In 1945 Roth and Kvale¹ found that the rapid intravenous injection of 0.05 or preferably 0.025 mg. of histamine base produced attacks identical to the spontaneous attacks of which these patients complained and afforded an opportunity of observing the patient in an attack. They reported observations of this test on 9 normal subjects, 22 patients who were hyperreactors to the cold pressor test, 16 patients with well-established hypertension and 3 patients suspected of having pheochromocytoma.

Results were positive in the 3 patients suspected of having pheochromocytoma as evidenced by a sudden rapid rise in blood pressure which reached its peak at the end of 2 minutes and returned to the basal level in 5 to 10 minutes. The rise in 1 instance was 100 mm. Hg. more than the rise obtained during the cold pressor test. This elevation of blood pressure was accompanied by characteristic symptoms of a typical spontaneous attack in all 3 patients with pheochromocytoma. In all other persons studied the blood pressure following the dose of histamine rose to a level somewhat less than the elevation obtained by a cold pressor test. The tumors were removed successfully from the patients with pheochromocytoma and yielded from 50 to 682 mg. of crystalline epinephrine. During the postoperative period repetition of the histamine test gave negative results. One precaution which should be mentioned is that barbiturates and other sedatives have an inhibitory action on the cold pressor test and not on the histamine test. When observations are made after the

ANNUAL DINNER

The Annual Dinner of the American Heart Association will be held in the Vernon Room, Chalfonte-Haddon Hall, Atlantic City, New Jersey, 7 P.M., Saturday, June 4, 1949. Members are invited to bring their family and friends. Tickets for the Dinner are \$6.50 each and application blanks may be obtained by writing to the central office, 1775 Broadway, New York 19, New York.

patient has received sedatives, the results can be very misleading.

Tetraethylammonium Bromide

In 1947 LaDue, Murison and Pack² suggested an intravenous injection of 100 mg. of tetraethylammonium bromide as a diagnostic test for pheochromocytoma. In 1 case of pheochromocytoma and mildly persistent hypertension, similar levels of blood pressure were obtained with 0.025 mg. of histamine base or by intravenous administration of 400 mg. of tetraethylammonium bromide. With the latter drug the elevation of the blood pressure persisted for 15 minutes in contrast to the return to normal in 5 minutes following the injection of histamine. They felt that the use of tetraethylammonium bromide had one advantage over that of histamine in that the dangerously high levels of blood pressure could be controlled by having the patient sit up or stand. Therefore they suggested the use of a tilting bed or table in testing for the presence of a pheochromocytoma with tetraethylammonium bromide.

We have used this drug on 4 patients with proved tumors. In 2 there was little or no rise in the blood pressure in spite of the existence of a tumor; in 2 others there was a definite rise in the blood pressure. In 2 other cases a rise in blood pressure followed injection of tetraethylammonium bromide but the other tests gave negative results and no tumor was found at operation.

Methacholine Chloride (Mechoyl Chloride)

Guarneri and Evans³ used mechoyl in 1 case of pheochromocytoma. They injected 25 mg. subcutaneously and obtained the usual fall in blood pressure, a sharp rise within 2 minutes and a return to the basal level 15 minutes later. Associated with the rise in blood pressure were all the symptoms characteristic of an attack of paroxysmal hypertension due to pheochromocytoma. In addition, the patient experienced the side reactions to mechoyl, which include nausea, salivation, epiphora, sweating and dyspnea. These authors also gave the same amount of mechoyl to 7 normal subjects and 20 patients with hypertensive vascular disease. They concluded that the mechoyl test may be more reliable than the histamine test inasmuch as they noted no hyperreactors to mechoyl, while they found 5 hyperreactors to histamine. The question might be raised as to whether sedation played a role in some of their cold pressor and histamine tests.

Insulin Tolerance Test

Later in 1947 Goldner⁴ reported a case of pheochromocytoma with diabetes. He performed an insulin tolerance test on this patient and obtained a response similar to that obtained when epinephrine was given together with or shortly after insulin. He felt that such a test might indicate the presence of an adrenal medullary tumor in a patient with diabetes.

Piperidylmethyl Benzodioxane (933F)

Slightly later in the same year Goldenberg, Snyder and Aranow⁵ suggested the use of piperidylmethyl benzodioxane, one of the adrenolytic drugs previously investigated by Forneau. An adrenolytic drug would act directly on epinephrine in the circulating blood. If the hypertension was due to circulating epinephrine, the blood pressure should be significantly decreased by the intravenous administration of benzodioxane. If the hypertension was due to another cause, the blood pressure would still remain elevated. In many cases essential hypertension showed a purely pressor response to benzodioxane. By the intravenous administration of 10 mg. per square meter of body surface, they were able to establish the diagnosis of pheochromocytoma in 4 patients with persistent hypertension. This is an important contribution because it is especially difficult to diagnose adrenal medullary tumors asso-

ciated with persistent hypertension. In contrast, we found with this compound only a pressor effect in 2 patients with paroxysmal hypertension and proved tumors.

Cahill⁶ reported the diagnosis of pheochromocytoma in 3 children and 1 adult following the intravenous administration of benzodioxane because of the resultant significant decrease in blood pressure.

Dibenamine Hydrochloride (Dibenzyl-beta-chlorethyl Amine Hydrochloride)

Another adrenolytic compound was used by Spear and Griswold.⁷ Their patient was given dibenamine hydrochloride 7.0 mg. per kilogram of body weight intravenously in 300 cc. of 5 per cent glucose in physiologic saline solution over a period of an hour to lessen the possibility of toxic reactions. A significant decrease in the blood pressure was noted. At another time a histamine test gave positive results. On repetition of histamine tests at intervals of 6, 30 and 48 hours after the administration of dibenamine hydrochloride, no rise in blood pressure was noted at 6 hours and the rise in blood pressure at 30 and 48 hours was less than that before the administration of dibenamine hydrochloride. Furthermore, after the administration of dibenamine hydrochloride the paroxysmal elevations of blood pressure were eliminated for a period of 24 hours and the patient was symptom free for 72 hours. They suggested that this compound appears to be of value both in the diagnosis of a pheochromocytoma and in the preoperative preparation of the patient.

Because the adrenolytic compounds have a pressor effect when circulating epinephrine is not present, they are ineffective as an aid to diagnosis in cases of paroxysmal hypertension and their use may be misleading. In cases of markedly elevated blood pressure it is wiser to give tetraethylammonium bromide first. If blood pressure then decreases definitely, essential hypertension may be the diagnosis. On the other hand if blood pressure increases significantly, the presence of adrenal tumor can be confirmed at another time by the use of the adrenolytic drugs, benzodioxane or dibenamine if significant decrease of the blood pressure occurs. A rise in the blood pressure with tetraethylammonium bromide usually indicates the presence of a tumor but no tumor has been found on several occasions. If the hypertension is moderately severe, an adrenolytic drug may be used initially and the presence of the adrenal tumor will cause the blood pressure to fall.

In the patients with paroxysmal hypertension, histamine or mechoyl will produce a sharp rapid rise in blood pressure accompanied by spontaneous attacks. If diabetes is present, an insulin tolerance test may be helpful, although histamine and also probably mechoyl will demonstrate the typical syndrome under these circumstances.

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